REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the amendments above and comments below.

Claims 1-5, 7-14, 16-18 and 20-24 are pending in the subject application.

Claim 1 has been amended to correct a clerical error. The claim has also been amended to recite a disease "or condition" that effects kidney function. Claim 20 has also been amended to recite "condition." This latter amendment finds support in original claim 2, which recites several conditions, as well as diseases. Claims 21 and 24 have been amended to correct clerical errors and no substantive changes to these claims have been made. Claim 10 has been amended to clarify that the antibody recognizes and binds to native and intact modified albumin, but not to other polypeptides or peptides. Other amendments to the claims are non-substantive in nature and do not add new matter.

I. Objections to Claims 21 and 24

It is respectfully submitted that the amendments to claims 21 and 24 render these grounds of objection moot.

II. Rejection of Claims 1-5, 7-14, 16-18 and 20-24 Under 35 U.S.C § 112, Second Paragraph

Claims 1-5, 7-14, 16-18 and 20-24 stand rejected under 35 U.S.C § 112, second paragraph . The Examiner states that these claims are vague and indefinite.

This rejection is respectfully traversed as follows.

The Examiner states that the term "intact modified protein" as used in claim 1 is unclear because it is not clear how it differs from "fragmented albumin", since both are not detectable by conventional radioimmune assays. Applicant respectfully disagrees.

The term "intact modified protein" is defined in the specification as substantially full-length protein (p. 10, para. [53]), whereas fragmented albumin is defined as breakdown products having reduced size and/or hydrophobicity. it is respectfully submitted that the skilled practitioner can distinguish such polypeptides.

It is respectfully submitted that the amendments to the claims render the grounds of rejection set forth on page 3 of the Office Action moot.

Accordingly, the rejection of claims 1-5, 7-14, 16-18 and 20-24 under 35 U.S.C § 112 is respectfully traversed.

III. Rejection of Claims 8, 10, 18, 20 and 23 Under 35 U.S.C § 112, First Paragraph

Claims 8, 10, 18, 20 and 23 stand rejected under 35 U.S.C § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner states that the specification does not enable the skilled practitioner to detect intact modified protein with antibody or dyes. The Examiner also states that the definition of intact modified protein is inconsistent with that in the parent application. According to the Examiner, the prosecution history of the parent application shows that intact, modified protein is detectable by non-antibody means only. The Examiner also states that the specification teaches that only modified forms of the protein, but not intact, modified forms of protein are detectable by specific dyes. The Examiner concludes, therefore, that the specification is not enabling for detecting intact modified protein with antibodies or dyes.

Applicant respectfully disagrees with the Examiner's conclusion.

The parent application, which issued as 6,589,748 ('748 patent) July 8, 2003, not only discloses, but claims detection of intact, modified protein with antibodies and dyes. The following claims are copied from the '748 patent:

16. The method according to claim 14, wherein the modified protein is detected by an antibody that is specific for native and/or intact modified forms of the protein.

17. The method according to claim 16, wherein the antibody is specific for the modified protein.

24. The method according to claim 14 wherein the protein is albumin and the non-antibody assay comprises use of an albumin specific dye to test for native and intact modified albumin.

As can be seen above, there is no inconsistency in the manner in which Applicant is claiming the invention described in the present application and the manner in which the invention was claimed in the parent application.

It is respectfully submitted that the application supports the present claims. For example, it is taught that the modified protein of the invention, i.e., intact, modified protein (as defined on page 10, para. 53) "can be detected by a variety of methods." (p. 15, para. 79). The "modified protein can also be detected by use of specific dyes. Such methods are described by . . . " (p. 15, para. 82).

The specification also emphasizes that the intact, modified protein of the invention cannot be detected by "conventional" radioimmune assay. However, it is well-known in the art

how to generate antibodies, and antibodies that specifically recognize and bind to the intact, modified protein or that recognize and bind to both the intact, modified protein and the native protein (specific for intact, modified and native protein) can readily be prepared by the skilled practitioner using conventional, well-known methods. Indeed, the specification teaches development of such antibodies at pages 18-19.

Accordingly, the rejection of claims 8, 10, 18, 20 and 23 under 35 U.S.C § 112, first paragraph is respectfully traversed.

IV. Rejection of Claims 1-5, 7, 13, 14, 16, 17, 20, 21 and 23 Under 35 U.S.C § 112, First Paragraph

Claims 1-5, 7, 13, 14, 16, 17, 20, 21 and 23 are rejected under 35 U.S.C § 112, first paragraph. The Examiner states that the specification enables a method for assessing therapeutic effectiveness of an agent for the treatment kidney disease by detecting intact and intact modified albumin in a urine sample of a patient, but does not enable a method for diagnosing kidney disease by detecting the sum of any other intact and intact modified protein in the urine of a patient. Applicant respectfully disagrees with the Examiner's conclusion.

The specification teaches that proteinuria, and in particular, albuminuria, is a marker of kidney disease.(p. 1, para. 4). Proteinuria is a condition wherein various proteins in concentrations greater than 0.3 g in a 24 hour urine sample or greater than 1 g/L in a random urine collection on two or more occasions at least six hours apart are detected. **(See pp. 1443 and 1445 of Stedman'sMedical Dictionary, copy enclosed)**. Thus, protein is known to exist in urine when the kidneys are not functioning properly.

The specification also teaches, and it is known in the art, that proteins are normally excreted as a mixture of native protein and fragments that are specifically produced during renal

passage (p. 3, para. [08]). In normal individuals, most of the protein in urine is fragmented. **(See Osicka, Clin. Sci. (Lond.), 1997, 93(1):65-72, copy enclosed)**. However, patients with kidney disease show an imbalance of intact protein versus fragmented protein in their urine, having much more intact protein than fragmented protein. The imbalance that is known to occur in kidney disease is used herein to diagnose renal dysfunction. Thus, detection of intact protein or intact, modified protein, regardless of which particular protein it is, is an indication of renal failure. The skilled practitioner does not need to know which, if any particular protein is associated with a particular disease or condition, because the presence of any intact protein or intact, modified protein in the urine is an indication of a renal condition.

Applicant has discovered that conventional assays for detecting protein in urine, such as albumin, fail to detect all forms of the protein that may be present. As a result, conventional methods fail to detect a protein imbalance until the pathological condition has progressed to a point where the kidneys are actually irreversibly damaged. Applicant's studies have shown that when the kidneys are not functioning properly, e.g., as a result of kidney disease, the urine contains both intact and intact modified proteins, as well as fragmented proteins. However, the intact modified proteins are not typically detected by conventional screening methods, such as RIA. Consequently, kidney disease cannot be diagnosed until enough of the intact (native) protein is present in the urine to be detected, which most often does not occur until the later stages of disease when irreversible kidney damage has already occurred. (p. 14, para. [76])

The specification teaches that normally functioning kidneys excrete predominantly fragmented proteins, whereas diseased kidneys excrete intact and modified proteins. The specification also teaches the detection of modified intact albumin *as an example* of a protein known to be associated with kidney disease. ("In the method of the invention, albumin is used herein only as an example of a protein to be detected in urine." (p. 14, para [75]). However, the

specification discloses that the methods of the invention can be applied to any protein in the urine, such as for example, globulin, euglobulin, pseudoglobulin, fibrinogen, alpha 1 glycoprotein, alpha 1 lipoprotein, ceruloplasmin, alpha 2 19S glycoprotein, beta 1 transferrin, beta 1 lipoprotein, immunoglobulins A, E, G and M, horseradish peroxidase, lactate dehydrogenase, glucose oxidase, myoglobin, lysozyme, protein hormone, growth hormone, insulin, parathyroid hormone. [p. 10, para. [53] and original claim 7].

Enclosed herewith is a declaration of the inventor, Dr. Wayne Comper, which discloses data obtained from analysis of two other proteins, transferrin and IgG, in urine samples obtained from control and diabetic rats. As can be seen from the bar graph attached to the declaration, the profile of transferrin in urine of control mice and diabetic mice obtained by the methods of the invention is significantly different from that observed using conventional methods of protein measurement. Immunoassay detected significantly less transferrin in both control and diabetic mice than was detected by the method of the invention. Moreover, there is a significant increase in the amount of modified (Ghost) transferrin in diabetic mice, while the amount of transferrin detectable by immunoassay increases only slightly. If measured by conventional methodology, the increase in amount of transferrin in the urine of the diabetic animals would have gone undetected or would have appeared to be insignificant at best.

In another experiment, the content of IgG in the urine of control and diabetic rats was measured six weeks after the induction of diabetes. As with transferrin, the IgG profile was remarkably different in both control and diabetic rats when measured by the method of the invention in comparison to measurement by conventional immunoassay. In both control and diabetic animals the amount of ghost IgG was at least ten times higher than the amount of IgG detectable by immunoassay. The amount of ghost IgG in control animals was not significantly

different from that observed in the diabetic animals at six weeks, indicating that the effect on IgG in diabetic animals is delayed in comparison to transferrin.

Applicant's data clearly show that the methods of the present invention provide urinary protein profiles that are significantly different from those obtained using conventional methods for measuring protein, e.g., immunoassay. The methods of the present invention provide a much more accurate measurement of protein content in urine. Moreover, the data also show that detection of ghost protein by the methods of the invention provides an early indicator of renal disease.

Accordingly, the rejection of claims 35 U.S.C § 112, first paragraph is respectfully traversed.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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